

Osteogenic Sarcoma in Children

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■ *One hundred and thirty children less than 16 years of age with pathologically verified osteogenic (skeletal) sarcoma were seen during a 30-year period (1925-1955) with a minimum follow-up of ten years. This age group represents 23.6 per cent of the authors' total experience with skeletal sarcoma. The absolute survival for the entire series was 18.5 per cent at five years and 16.2 per cent at ten years.*

No child with an osseous tumor elsewhere than in an extremity had long-term survival. Amputation was the only "curative" method of therapy; 23 per cent of patients so treated were alive at five years and 20 per cent were alive at ten years. Radiation was never "curative" when used as the sole method of therapy, and treatment failure was higher in the group of patients who were treated with preoperative irradiation and then amputation than in the group treated by amputation alone.

Prognosis varied with the size of the tumor—the smaller the better. The most important factor in prognosis was the histologic subgrouping of osteogenic sarcoma. No evidence was found to support a belief that there are considerable differences between skeletal sarcomas in children and in adults.

OSTEOGENIC SARCOMA is the commonest primary malignant neoplasm of bone and, contrary to common belief, long survival is sometimes obtainable. Many of these tumors occur in the pediatric age where optimal treatment is too frequently modified by emotional considerations of the parents and by an air of hopelessness on the part of the physician—these deterrents at a time when radical surgical therapy offers the only hope.

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For many years the opinion has been held that the prognosis for osteogenic sarcoma is worse in children than in adults.¹ Recently, Hayles and co-workers⁴ offered evidence that age did not affect prognosis.

We⁵ recently recorded our findings in a 30-year experience with osteogenic sarcoma in patients of all ages. We suggested that the term *osteogenic sarcoma* be used in the generic sense or discarded. The word *osteogenic* in this usage implies a derivation from primitive mesenchymal tissue which is normally destined to form skeletal connective tissue components. The classification includes the

following categories: primary osteosarcoma, primary chondrosarcoma, primary fibrosarcoma, parosteal osteogenic sarcoma and secondary tumors arising in bone altered by preexisting disease or previous treatment. Schajowicz⁶ suggested that the term *skeletogenic* be substituted for *osteogenic* since the latter term is sometimes used ambiguously as an interchangeable designation for osteosarcoma. Dahlin,² for instance, uses *osteogenic sarcoma* for osteoblastic bone sarcoma, where we use *osteosarcoma*.

Material

This report of 130 patients with osteogenic sarcoma, all under 16 years of age, represents 23.6 per cent of the total experience⁵ with this neoplasm at the Memorial Center in the period 1925-55.

Pathology

The diagnosis was established in all cases after review of the clinical setting, the roentgenograms and the gross and microscopic material. The 130 tumors were subgrouped as follows: Osteosarcoma, 99 cases; chondrosarcoma, 16; fibrosarcoma, 8; parosteal osteogenic sarcoma, 4; osteogenic sarcoma arising in irradiated bone, 2; and secondary chondrosarcoma, 1. (See Table 1.)

Age and Sex

The age range was from 4 to 15 years (Chart 1). The youngest patient in each histologic subgroup was as follows: Osteosarcoma, age 4; fibro-

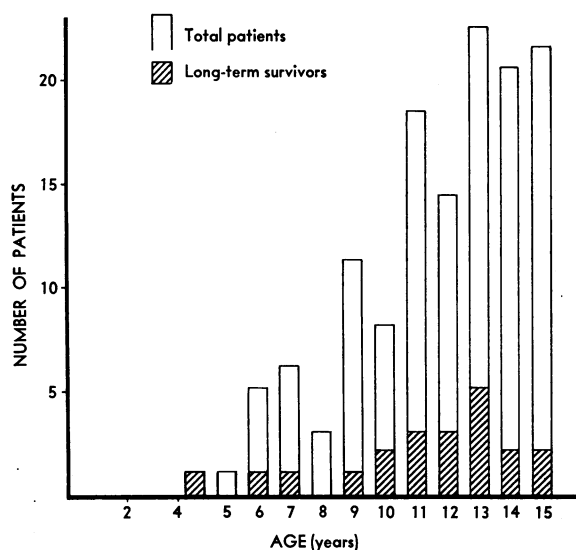


Chart 1.—Age incidence—osteogenic sarcoma in children.

TABLE 1.—Osteogenic Sarcoma in Children—Site and Histologic Subgroup—Asterisk (*) indicates Long-Term Survivors

Bone	Total	Osteosarcoma	Chondrosarcoma	Fibrosarcoma	Parosteal Osteogenic	Secondary Irradiation	Secondary Chondrosarcoma
Femur	75	62	6	4	3	0	0
Tibia	25	21	3	1	0	0	0
Humerus	16	11	2	2	0	0	0
Pelvis	3	0	0	0	0	1	0
Fibula	2	1	0	0	0	0	0
Mandible	2	0	0	0	0	0	0
Os calcis	2	1	0	1	0	0	0
Miscellaneous	5	0	2	0	0	0	0
Ulna	1	0	1	0	0	0	0
Scapula	1	0	0	0	1	0	0
Skull	1	0	0	0	0	0	0
Rib	1	0	0	0	0	1	0
Vertebra	1	1	0	0	0	0	0
Totals—							
Children	* 21 of 130 (16.2%)	* 10 of 99 (10%)	* 4 of 16 (25%)	* 3 of 8 (37.5%)	* 4 of 4 (100%)	* 0 of 2	* 0 of 1
Adults	* 77 of 422 (18.1%)	* 18 of 159 (11.1%)	* 26 of 123 (21.1%)	* 9 of 52 (17.4%)	* 13 of 18 (72%)	* 4 of 20 (20%)	* 5 of 11 (45.5%)

sarcoma, age 7; chondrosarcoma, age 9; osteogenic sarcoma arising in irradiated bone, age 9; secondary chondrosarcoma, age 11; parosteal osteogenic sarcoma, age 12. Male and female patients were in equal number.

Site

Most (91.5 per cent) of the neoplasms in this series originated in the long bones, and 83 per cent of these extremity tumors arose in the metaphyseal region (Chart 2). The lower extremity contained 80 per cent and the upper extremity 13 per cent. Only 7 per cent of the tumors were at sites other than an extremity. Sixty per cent were located about the knee.

Ninety per cent of all tumors were at three osseous sites—femur, tibia and humerus. More than half (75) of the total number of tumors were located in the femur (3 proximal, 13 diaphysial, 59 distal). There were 25 tumors in the tibia (19 proximal, 3 diaphysial, and 3 distal) and 16 in the humerus (13 proximal, 3 diaphysial).

Signs and Symptoms

Pain was the initial and most distressing symptom in 75 per cent of cases. A swelling was the first symptom in 15 per cent. A third and infrequent initial symptom was a disability such as limping or restriction of motion. Persistent pain, swelling or both demand roentgenographic examination of the affected bone. A fracture was the presenting symptom in two patients and later occurred in 17.

The average time from the first symptom to diagnosis was three months with a median of two months and a range of from less than 1 to 24 months. Only seven children had symptoms for more than six months before treatment was begun.

A swelling was the commonest (90 per cent) finding on physical examination. Redness, point tenderness, increased local heat and limitation of joint motion were noted in half of the patients.

Trauma

Several patients gave a history of minor trauma to the involved area. (We believe that the injury directed the patient's attention to a lesion already present.)

Laboratory Studies

Serum alkaline phosphatase is the only laboratory determination which may be significantly al-

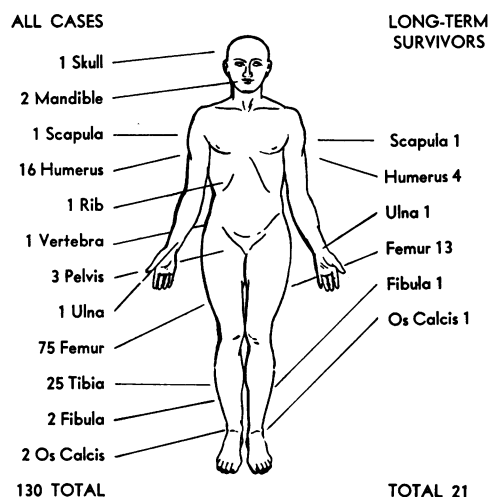


Chart 2.—Location of osteogenic sarcoma in children.

tered in patients with osteogenic sarcoma. Of 98 patients initially tested, 23 had elevated levels (more than 15 Bodansky units in children). Of 75 patients with normal values when sarcoma was first diagnosed, five had later elevations. Two of the 21 with long-term survival had high serum alkaline phosphatase before treatment (18.3 and 20 Bodansky units) and in these cases the level reverted to normal after therapy. Only nine children had alkaline phosphatase values greater than 30 Bodansky units terminally, ranging from 31.4 to 95.4.

In our experience the frequency of alkaline phosphatase elevations and the range of abnormal values associated with osteogenic sarcoma are about the same for children as for adults, with the exception that sarcomas arising in bone affected by Paget's disease occur only in adults and in these patients there is usually pronounced elevations of serum alkaline phosphatase.

Associated Conditions

Pathogenesis and the cause of osteogenic sarcoma remain unexplained and in only three cases in this series of children did the lesion originate in bone altered by preexisting disease or previous treatment. Two children had received radiation therapy, one for a neuroblastoma and the other for a humeral bone cyst, and in both cases an osteogenic sarcoma developed in the treated bone, six years later in one case, eight years in the other. In another case, that of a boy with multiple osteochondromas since age 4, a secondary chondrosarcoma developed in one osteochondroma at age 11.

Metastasis

Pulmonary metastasis was demonstrated roentgenographically at the time of admission in 13 per cent of the children in this series. X-ray films of the chest are therefore mandatory in all cases before definitive treatment is begun. Metastatic lesions in the lungs were demonstrated in at least 91 per cent of patients at the time of death, and most of these patients died of respiratory failure.

Metastasis to bone was rarely apparent (1 per cent) when the diagnosis of sarcoma was first established, but such lesions were identified later in 25 per cent of patients who died of sarcoma.

Other sites of metastasis, such as lymph nodes, soft tissue, heart, brain and ovary were noted in 9 per cent of patients who died of sarcoma.

Sequellae of metastasis included paraplegia in five patients with vertebral metastasis and pneumothorax in one patient with pulmonary metastasis.

Treatment

One hundred and three children were treated surgically with curative intent and in all but two cases amputation was eventually carried out. Fifty-four (52.5 per cent) of the surgically treated patients received preoperative irradiation from various sources—radium element packs (in the years 1925-1936), orthovoltage (1928-1955) and supervoltage (1947-1955). A tumor dose varying from 1,500 to 12,000 rads was complemented by surgical ablation one day to many months after completion of radiation therapy. Nine children were treated solely by radiotherapy. Eighteen children with distant metastasis received only palliative therapy.

Surgical ablation is the only curative therapy for a skeletogenic sarcoma. An extremity tumor should be amputated by removing the entire bone and sufficient soft tissue to minimize the liability of recurrence. For sarcoma of bone in non-extremity locations, radical excision of the affected bone and the surrounding soft tissue is recommended.

Palliative therapy of a bone sarcoma is rarely indicated when pulmonary or osseous metastatic lesions are present. Severe pain may be lessened by irradiation and occasionally amputation may be justified for an ununited fracture or a massive tumefaction.

Irradiation as the sole method of therapy was

never curative; preoperative radiation therapy has been advocated by some clinicians, but no evidence was found in the present series to support this recommendation.

Survival

The absolute survival for the entire series of 130 osteogenic sarcomas was 18.5 per cent at five years and 16.2 per cent at 10 years. Only one patient was lost to follow-up, and for statistical purposes was presumed dead as a result of sarcoma.

Of the 103 patients surgically treated, one died in the postoperative period. Twenty-four children (23.3 per cent) were alive at five years and 21 (20.4 per cent) were alive at 10 years. Six patients were alive and well more than 20 years after treatment. Of those who died of sarcoma, none died more than seven years after diagnosis.

All of the long-term survivors had had amputation. In six cases in which conservative surgical excision was employed, there was local recurrence of sarcoma; then in three of those cases in which the tumors were in an extremity, amputation was done and two of the children then had long survival without recurrence. The three patients with non-extremity tumors (two mandible, one ilium) were retreated by reexcision (one to three times) unsuccessfully.

Radiation therapy brought about no "cures" when used as the only treatment. Survival after irradiation ranged from three months to 26 months after diagnosis, with an average and median interval of 12 months.

Treatment failures were more frequent in patients receiving preoperative irradiation and amputation than in patients treated solely by amputation. Of 47 patients who were treated primarily by amputation, 15 (32 per cent) were alive at five years, and 12 (25 per cent) were alive at 10 years. Of 54 children who first had radiation therapy and then amputation, nine (16.7 per cent) were alive at both five and 10 years after diagnosis. The median survival time for children in whom treatment failed was 14 months when the treatment was amputation alone, and 11 months when it was irradiation and amputation.

Survival was higher when the sarcomas were in peripheral locations such as the long bones than when they were at other skeletal sites, such as the skull, vertebrae and ribs where radical operation cannot be done. No long-term survivals

were noted for skeletogenic sarcoma in the following locations: Tibia, pelvis, mandible, skull, rib or vertebra. The osseous sites of sarcoma in the 21 cases in which there was long-term survival were as follows: Femur, 13 (12 distal, 1 diaphysal); humerus, 4 (3 proximal, 1 diaphysal); and one each in the fibula, ulna, scapula and os calcis.

The single most important factor in prognosis in children with a skeletogenic sarcoma was the histologic type (Table 1). The majority of tumors in this series were osteosarcomas and the long-term survival associated with them was the poorest (10 per cent). The survivals in the other three primary subgroups were as follows: Chondrosarcoma, 25 per cent; fibrosarcoma, 37 per cent; parosteal osteogenic sarcoma, 100 per cent. These absolute survival rates in children are nearly identical with the end-results in adults with osteogenic sarcoma (Table 1).

A thoracotomy was performed in two patients with unilateral lung metastasis. One patient was alive and well at last report, 15 years after lobectomy and 20 years after the diagnosis of fibrosarcoma of the proximal humerus (excised four times before amputation). The other patient died with sarcoma three years after lobectomy and six years after disarticulation of the hip joint for an osteosarcoma of the femur.

Osteosarcoma in Children and in Adults

Seventy-five per cent of the skeletogenic sarcomas in the children in the present series were classified as osteosarcoma. This is twice the proportional incidence of osteosarcoma in adults (37.5 per cent) and may be explained in part by an older average age of patients with chondrosarcoma and fibrosarcoma and the absence of Paget's sarcoma in children. In addition, few sarcomas in children were located in the head and trunk. At these sites chondrosarcoma is more frequently encountered, and this histologic subgroup is less common in children than in adults.

Prognosis can be related to the tumor size—the smaller the sarcoma, the more favorable the prognosis—both in children and in adults. In this series of 99 osteosarcomas, there were only two sarcomas 5 cm or less in size and in both these cases long-term survival was brought about by operation. In none of the cases in which the lesions were more than 15 cm in diameter was long-term

survival achieved. Grading of the tumors according to Broders' method was not useful in prognosis in osteosarcoma, either in children or in adults.

Definitive treatment, consisting of biopsy followed by amputation within one month, without interval resection or irradiation, resulted in a 16 per cent five-year survival and a 13 per cent long-term survival for osteosarcoma in children. These end results are similar to those observed in our experience with adults.

In other parameters of comparison, no essential differences between children and adults were noted. The local recurrence rate ranged from 15 to 20 per cent for extremity tumors and 85 to 100 per cent for sarcomas in an axial location. The incidence of late failures (death due to sarcoma more than five years after diagnosis) was similar (2 to 4 per cent) for children and adults with osteosarcoma.

Comment

In light of the long-term survival rate for osteogenic sarcoma in children achieved by radical ablative surgical operation—23 per cent at five years and 20 per cent at 10 years—the often expressed opinion that prognosis is extremely poor in young people with osteogenic sarcoma cannot be accepted. Pessimism should never influence a therapeutic decision in favor of irradiation in lieu of radical ablative operation. A delay of definitive surgical treatment to permit preoperative irradiation is not justified by the end results in this series.

Children and adults should be treated similarly for osteogenic sarcoma. This study has revealed no dissimilarity in the end results of treatment relative to age. There is a difference, however, in the incidence of the histologic subgroups in children and adults.

The psychological trauma of amputation is far greater for the parent than for the child; it has been our experience that children will readily accept the decision for amputation and can be easily rehabilitated as amputees. Whatever fleeting comfort the parents may get from a recommendation for conservative resection or irradiation must be measured against the knowledge that it is at the expense of depriving the child of one chance in five of "cure."

The findings which we have reported are similar in most respects to those in a series of 129 osteogenic sarcomas (*osteosarcoma* in our nomencla-

ture) in children at the Mayo clinic reported by Hayles and coworkers.⁴ They reported one patient with osteosarcoma treated only by radiation therapy to be alive and well for 34 years. We had no "cure" by irradiation; although we at first thought we might have, on pathologic review the lesion was reclassified as a chondroblastoma. There is no apparent explanation for the pronounced dissimilarity between the Mayo series and ours in the survival rate of patients with tibial sarcomas. In the Mayo series the survival rate associated with lesions at that site was better than average (40 per cent) whereas we had no survivors. Also, the Mayo group considered histologic grading of

osteosarcoma to be useful in prognosis, and in our experience it was not.

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